REMARKS

The Office Action of May 18, 2004 objects to applicant's amendment of July 30, 2003 as not fully responsive on the basis that there were several prior art rejections stated in the action of December 3, 2003, that were not addressed. Applicant apologizes for any inconvenience that this oversight may have caused and herewith addresses the outstanding rejections. The previous arguments regarding the Section 112 rejections, Heimberger (US 3,625,979) and Daeyaert (US 6,150,360) are not repeated herein.

Additionally, however, in reviewing the application to address the outstanding rejections, applicant noted some issues pertaining to the claims and thus, an amendment has been presented. The treatment of the claims is first discussed below, then the outstanding rejections.

Treatment of the Claims

It is gratefully acknowledged that at page 14 of the previous action, the Examiner noted that claim 77 is distinct and allowable.

For the Examiner's convenience, a complete listing of all claims is set forth herein. Claims 66-780 have been further amended to correct typographical errors, i.e., the article "a" was replaced with "an" preceding "enantiomer" in claims 70-78, the comma following "salt" was deleted, the reference to stereoisomer and prodrug in claim 73 was deleted (as per the amendment of July 30, 2003).

Additionally, there was confusion regarding antecedent basis in claims 66 and 70 that was corrected. In particular, claim 66 recited selections for the variables R^{12} and R^{13}, but the moiety $N(R^{12})(R^{13})$ was missing from the claim. Also, in claim 70, a selection for R^{14} was recited although the group $N(R^{12})(R^{13})$ was defined such that R^{14} was no longer a variable. These issues have been addressed herein and further, applicant has amended the claims such that Z and R_{11} are not unsubstituted amino ($-NH_2$). Such recitations for Z and R_{11} are supported at pages 10-14 and 18-27 of the specification. This amendment is not made in response to a prior art rejection but is made to provide greater clarity to the claim and aid in the examination process.

New claims 96 through 99 are added to recite the invention in alternative ways. Claim 99 is a method of use claim.

Outstanding Rejections

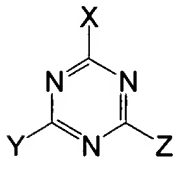
Besides relying on Heimberger and Daeyaert, the Office Action of December 3, 2003, raised rejections based upon previously-cited references Schmitz (US Pat. No. 3,290,305), Winter (US Pat. No. 3,867,383), Hoppe (US Pat. No. 4,617,390), Newton (US Pat. No., 5,062,882), and Raspanti (US Pat. Nos. 5,346,691, 5,759,525, 5,801,244), as well as newly-raised references Cyba (US Pat. No. 3,590,042) and Henkin (US 6,288,228).

It is noted that at page 11 of the Office Action, it is emphasized that all Section 102 rejections based on the following references were obviated and/or rendered moot, *i.e.*, Schmitz (US Pat. No. 3,290,305), Winter (US Pat. No. 3,867,383), Hoppe (US Pat. No. 4,617,390), Newton (US Pat. No., 5,062,882), and Raspanti (US Pat. Nos. 5,346,691, 5,759,525, 5,801,244). These references are now cited under Section 103(a). Also, Cyba is raised under Section 102, and Henkin under Section 103.

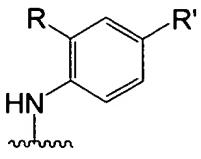
Applicant will first review the prior art, and then discuss why an obviousness conclusion is inapplicable.

Schmitz

Schmitz describes compounds having the formula



,wherein Z is in each case chlorine, and X and Y can be selected from amino acid groups and Y may also be chlorine or an amine group. The amino acid groups recited for X and Y include aminobutyric acid, dodecyl-aminobutyric acid, dodecyl-sulfanilic acid, sulfanilic acid, dodcecyl glycine, and where they include a phenyl group, the X and Y groups may be selected from:



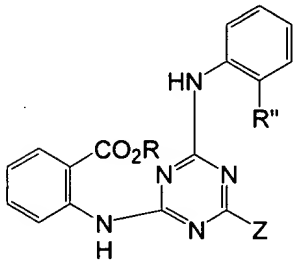
, wherein R can be H, C_8 alkyl, or C_{12}alkyl, and R' can be H, $-SO_3H$, or $-CO_2H$.

These compounds are reportedly useful as *anti-fungal agents* and/or *disinfectants*.

Schmitz does not show or suggest compounds having a meta-substituted aniline on the triazine group, or otherwise suggest any meta substituents on the phenyl group.

Winter

Winter recites compounds having the formula,

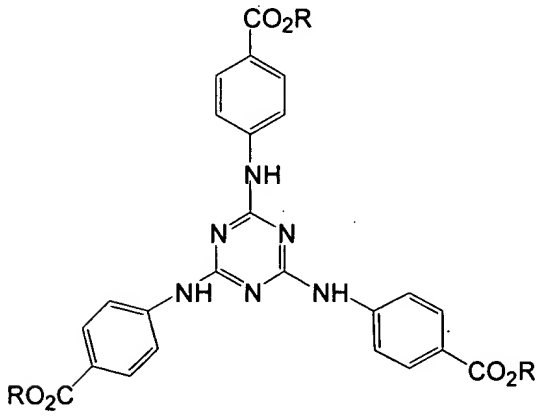


, wherein R" is H or CO_2R and R is H or lower alkyl. Reportedly, these compounds are useful as *cardiovascular* agents.

Winter does not show or suggest any meta substituents on the phenyl group.

Hoppe

Hoppe recites compounds having the formula,



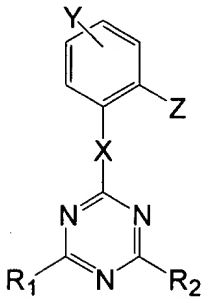
, wherein each of the R groups is a C_6-C_{12} alkyl or polyoxyethylene radical.

Reportedly these compounds are useful as *sunscreen* agents.

Hoppe does not show or suggest any meta substituents on any of the phenyl groups. Also, it is noted that all the compounds of Hoppe show three NH-phenyl groups on the triazine; thus, Hoppe does not allow for substitution with a non-aromatic NH-alkyl, for example, or a hetercyclic ring.

Newton

Newton discloses the genus of compounds having the formula,

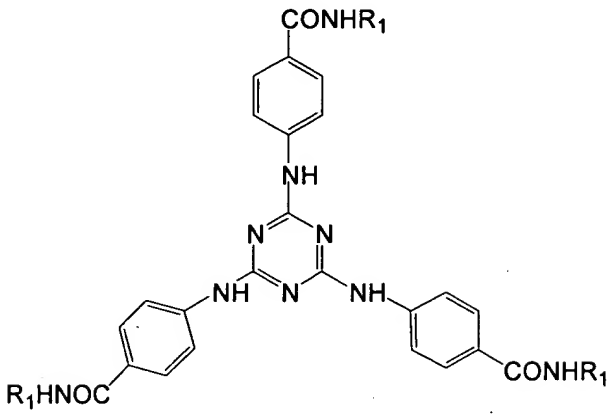


, wherein Z is a mandatory substituent, typically a group COR^3, wherein R^3 is alkoxy (alkoxycarbonyl group). Notably, in each of the Examples save one, Newton shows X as being an oxygen atom. The only aniline group shown in Newton is Example 19 wherein Z is CO_2Me and Y is H. Accordingly, Newton does not suggest a meta-substituted aniline group on the triazine. Additionally, with regard to other-than aniline chemotypes, e.g., wherein X is –O-, Newton shows meta substituents of Me (Ex. 16), hydroxy (Ex. 32), triazinyloxy (Ex. 33), methoxy (Ex. 49), benzo-fused ring (Ex. 50), $N(Et)_2$ (Ex. 55), and chloro (Ex. 60). In each of these examples, however, the mandatory ortho-substituent (Z) is CO_2Me or CHO. In the instant claims, neither R^7 nor R^8 allows for selection of CHO or alkoxycarbonyl.

The Newton compounds are reportedly useful as *herbicides*.

Raspanti

Several Raspanti patents are cited each of which are similar to the above Hoppe case. The Raspanti compounds are, as in Hoppe, useful as *light stabilzers and/or sunscreen* agents and have the formula,



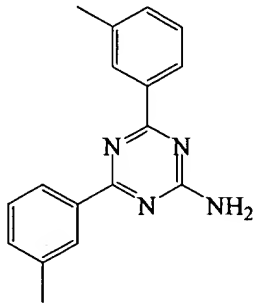
, wherein each R_1 is alkyl or cycloalkyl.

None of the Raspanti cases shows or suggests any meta substituents on any of the phenyl groups. Also, as with Hoppe, Raspanti shows three NH-phenyl groups on the triazine and does not allow for substitution with a non-aromatic NH-alkyl, for example, or a hetercyclic ring.

Cyba

Cyba discloses a composition useful as additives for plastics, polymers, resins, etc., whereby flameproof or fire-retardant properties are added. The composition includes a combination of a halo-substituted polycyclicdicarboxylic acid and a triazine. The Office Action relies upon column 4, lines 34 and 54 to reject the instant claims under Section 102. At these points, Cyba discloses compounds having the formulae:

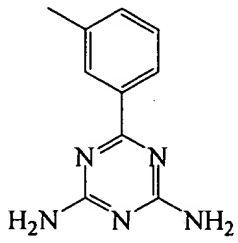
Line 34:



2-amino-4,6-di-(m-tolyl)-s-triazine

and

Line 54:

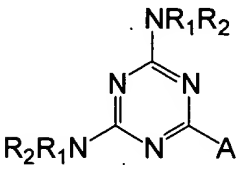


2,4-diamino-6--(m-tolyl)-s-triazine.

As can be seen, in Cyba the phenyl group is *directly* attached to the triazine not via a linker N, O, S, or C atom. Thus, for this reason alone, Cyba does not anticipate. No amendments to the claims are needed to distinguish Cyba.

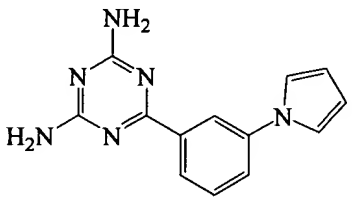
Henkin

Henkin shows angiogenesis inhibitors having the formula,



, wherein A is a heterocyclo, heterocycloalkyl or cycloalkyl group (not aryl) *directly* attached to the triazine, or group B-L-Y, and B and Y are cyclic groups which can be aryl. Notably, R_1, R_2, R_3 and R_4 are not aryl. Thus, Henkin in even its broadest genus does not disclose compounds falling in the instantly-claimed genus as Henkin does not show a phenyl group attached to the triazine via a linker group as "V" herein.

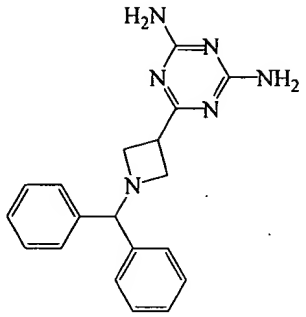
Column 3, line 17 and Example 4 are identified by the Office Action as pertinent. Here, Henkin shows:



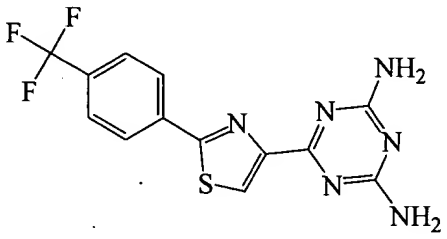
6-[3-(1H-pyrrol-1-yl)phenyl]-1,3,5-triazine-2,4-diamine

As can be seen, the phenyl group is directly attached to the triazine not via a linker N, O, S, or C atom.

Other representative compounds of Henkin include:



6-[1-(diphenylmethyl)-3-azetidinyl]-1,3,5-triazine-2,4-diamine (col. 3, line 13)



6-[2-[4-(trifluoromethyl)phenyl]-4-thiazolyl]-1,3,5-triazine-2,4-diamine (col. 3, line 66).

Applicant's Invention is Not Obvious in View of the Cited References

At the outset, applicant submits that the cited references should not be considered under Section 103 as they are not in an analogous field of compounds useful as p38 inhibitiors and/or anti-inflammatory agents. The Office Action acknowledges that "pharmacological activity in general is a very unpredictable field." (12/03 Action at p. 6). Additionally, the Office Action argues that even in the field of inflammatory diseases, "[t]here is no evidence in the prior art that all these diseases are equivalent." (Action at p. 8.) Certainly then, references outside the field of inflammatory diseases, and even more compelling, references outside the field of treating human conditions, such as herbicides (Newton), light stabilizers and sunscreens (Hoppe and Raspanti) and flame-retardant additives (Cyba), are not "reasonably pertinent to the particular problem with which the invention [is] concerned." MPEP 2141.01(a). [1]

[1] The concept of non-analogous art is applicable with regard to Section 103, but not Section 102.

It cannot be said that these references are analogous simply on the ground that they pertain to compounds having a biological effect. It stretches the concept of "analogous art" too far to suggest there is a "compound biological effect art" to which a scientist may look for guidance. *Compare In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1445-46 (Fed. Cir. 1992) (cited in MPEP § 2141.01(a)) (where the invention pertained to a hose clamp that used a particular type of hook, the Board looked to the garment industry to find a hook like the applicant's hook, and it argued the garment reference was analogous because it was in the "hook art." The Federal Circuit rejected this position and held that the reference was not analogous because it was not reasonably pertinent to the particular problem with which the inventor was concerned.) *See also Wang Labs v. Toshiba Corp.*, 993 F.2d 858, 26 USPQ2d 1767, 1773 (Fed. Cir. 1993) (reference relating to a single in-line memory module {SIMM} for an industrial controller was not analogous to applicant's invention pertaining to a SIMM for a printed circuit board of a personal computer even though *both pertained to SIMMs*).

Applicant for this reason requests that the Section 103 rejections be reconsidered and withdrawn.

However, even if the references were considered analogous, they do not provide a basis to reject the claims herein. The Office Action argues that the cited references each show different types of trisubstituted triazines, that these are "closely-related" compounds that are "positional isomers", and that based on these conclusions and various cases cited in the Action, evidence of unexpected or superior properties is required.

Applicant submits that the concept of positional isomerism does not apply here as this case involves novel pharmaceutical compounds with a new utility. However, before addressing that point, it is noted that the Office Action does not individually evaluate the concept of "positional isomerism" with regard to each of the references. However, the concept (even if applicable) would not be pertinent with regard to Hoppe and Raspanti (as each of these show three moieties of -NH-phenyl attached to the triazine), nor with regard to Cyba or Henkin (as each of these show phenyl rings *directly* attached to the triazine, and not via a linker atom), or with regard to Newton which involves a herbicidal use, clearly not an analogous field. This leaves consideration of Schmitz (disinfectants) and Winter (cardiovascular agents) for evaluating the positional isomerism argument.

Applicant submits the concept of positional isomerism finds no place in this pharmaceutical case involving a new utility over the cited art. The cited cases do not support the position that a *prima facie* case of obviousness can be established based on positional isomerism in the pharmaceutical industry where a new utility is being asserted. Rather, the only case cited in the Action that relates to the pharmaceutical industry (*In re Englehardt*), supports applicant's position herein, *i.e.*, that the compound's utility must be considered in drawing a conclusion under Section 103.

Indeed, each of the cases cited in the Action support this position. For example, in *In re Crounse*, 150 USPQ 554 (CCPA 1966), the applicant attempted to claim a monoazo compound useful as a water-insoluble dyestuff with a red color. The prior art disclosed a monoazo compound useful as a water insoluble dyestuff having a red-orange color that had the exact same structure as applicant's compound, save the ring position of the exact same amide and methoxy moieties. *Id.* at 555. The court noted that a section 103 conclusion requires the consideration of all *the properties* of the compounds and an analysis of all the circumstances. In that case, in rejecting the claim the court specifically relied upon findings that the two compounds were used for the same purpose, had identical ratings on a number of properties, and were made in the same way, *e.g.*, the court stated: "they possess identical ratings as to properties considered essential, i.e., resistance to fading and to dry-cleaning with perchloroethylene; 4-7) they have identical ratings as to other properties of washing in the presence, and the absence of chlorine bleach, resistance to discharge printing and to strong alkali, 8) the claimed compound is producible in the same manner as are the monoazo dyestuffs of Fischer, ...the manner of use is the same" and so forth. *See Id.* at 557.

Thus, fundamental to the decision in *In re Crounse* was that the compounds possessed identical properties.

Similarly, in *In re Finley*, 81 USPQ 383 (CCPA 1949), both the claimed compound and the prior art compound were used for the same purpose as a lubricant additive. *Id.* at 384. The claimed compound apparently was a homolog of the prior art compound, used for the same purpose and made in the same way. *Id.* at 385.

In E*x parte Henkle*, 130 USPQ 474 (Bd. Pat. App. 1960), no new utilities were asserted for the claimed compounds but instead, it was alleged they were useful as intermediates. *Id.* at 475. In *In re Norris*, 84 USPQ 458 (CCPA 1950), the court was dealing with a structural isomer and stated that precedent "support[s] the rejection of a novel compound which is isomeric with compounds of the prior art, where the new compound is not shown to possess new and unexpected utilities." *Id.* at 461. No new utilities were recited in the Norris case, but again, it was alleged that the compound was useful as an intermediate.

The only case cited in the Office Action that pertains to the pharmaceutical industry is *Ex parte Englehardt*, 208 USPQ 343 (Pat. Bd. App. 1980), but this case supports applicant's position herein about the need to consider the compound's utility. *Englehardt* was a reissue case where the applicant was pursuing claims to a *method of using* a known compound, *i.e.*, amitriptyline, for treating depression. *Id.* at 349. Prior art disclosed that a drug imipramine was useful for treating depression, and the only difference in structure between imipramine and amitriptyline was that in amitriptyline, a carbon-carbon double bond of imipramine was saturated to a single bond. *Id.* at 348-49. Additionally, several prior art compounds known to be useful to treat depression had the same structure of amitriptyline, with the saturated C-C bond, save in those compounds an ethylene group was replaced with a thiol moiety. *Id.* at 349. Beyond this, there were reports in the case wherein various scientists noted that in view of the close similarity in structure between amitriptyline and imipramine, the former should be considered for use in treating depression, as with imipramine. In view of all the circumstances, the Board upheld the examiner's rejection of the claims.

Thus, *Ex parte Englehardt* underscores the need to consider utilities and the relationship between a compounds structure and properties. *See also* In re Papesch, 137 USPQ 43, 51 (CCPA 1963) ("from the standpoint of patent law, a compound and all of its properties are inseparable").

Accordingly, the above line of cases is inapplicable here because the applicant is not reciting the same utility as in any of the cited prior art patents. The new utility claimed herein is amply supported by applicant's specification which must be considered. *See* MPEP 2144.08 (B).

Moreover, the cases establish that particularly in the area of pharmaceuticals, the Examiner is required to consider the compounds' biological properties in assessing the obviousness of the claims. For example, in *In re Wagner*, 371 F.2d 877, 152 USPQ 552 (C.C.P.A. 1967), the court reversed a PTO conclusion of obviousness. There, the claims recited benzimidazole derivatives substituted with at least one lower alkyl group at two specific positions. The prior art taught benzimidazole derivatives having no substituents or bearing dimethyl substituents at two *other* positions of the ring. On appeal, the CCPA pointed out that there were eleven possible locations for placement of the methyl substituents. *Id.*, 152 USPQ at 559. It specifically rejected the PTO's finding that "the modification of a compound by the addition of one or more methyl groups is well known and thus obvious," stating that such general statements cannot support legal conclusions of obviousness. *Id.* at 883-84, 152 USPQ at 559. The Board erred, the court found, *by failing to take into account biological or pharmaceutical properties of the compounds. Id.* at 881, 152 USPQ at 557.

As indicated by *In re Wagner*, it is well known in the field of pharmaceuticals that small changes can have dramatic effects on biological activity. *See also Kawai*, 178 USPQ 167, 173 (CCPA 1973) ("minor changes in chemical compounds can radically alter their effects on the human body").

For the foregoing reasons, applicant submits that the Section 103 rejections must be withdrawn.

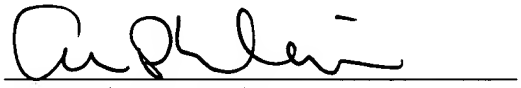
FEES

Applicant has added four new claims. It is not believed a fee is due because a greater number of claims were previously canceled. However, in the event a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

SUMMARY

In view of the foregoing, it is requested that the rejections be withdrawn and the case proceed to issuance. The Examiner is invited to contact the undersigned if it is believed prosecution could be expedited.

Respectfully submitted,



Anastasia P. Winslow
Attorney for Applicants
Reg. No. 40,875

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
609-252-6996

Date: June 16, 2004